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Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council trial

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Objective To compare the effect on the course of advanced prostate cancer of hormone treatment commenced on diagnosis with that deferred until clinically significant progression occurs.

Patients and methods Nine hundred and thirty-eight patients with locally advanced or asymptomatic metastatic prostate cancer were randomized either to immediate treatment (orchidectomy or luteinizing hormone-releasing hormone analogue) or to the same treatment deferred until an indication occurred. Follow-up and management were otherwise according to the participating clinician's normal practice. Information was collected annually on survival, local and distant progression, and major complications (pathological fracture, spinal cord compression, ureteric obstruction and extra-skeletal metastases).

Results Follow-up data were returned on 934 patients; 51 deferred patients died from causes other than prostate cancer before treatment was started (but only five of these presented at age <70 years) and 29 died from prostate cancer before treatment could be started. Treatment was commenced for local progression almost as frequently as for metastatic disease. Progression from M0 to M1 disease ($P<0.001$, two-tailed) and development of metastatic pain occurred more rapidly in deferred patients; 141 deferred patients needed transurethral resection for local progression compared with 65 treated immediately ($P<0.001$, two-tailed). Pathological fracture, spinal cord compression, ureteric obstruction and development of extra-skeletal metastases were twice as common in deferred patients. Of the patients who died, 67% did so from prostate cancer; 361 patients died in the deferred arm compared with 328 in the immediate arm ($P=0.02$, two-tailed), where 257 and 203 were deaths from prostate cancer, respectively ($P=0.001$ two-tailed). This difference was seen largely in M0 patients, with 119 and 81 deaths from prostate cancer, respectively ($P<0.001$ two-tailed).

Conclusions The results consistently favour immediate treatment, although some of the data, especially on M0 patients, are immature. The implications for management of advanced prostate cancer are discussed.

Keywords Prostate cancer, hormone treatment, deferred treatment

Introduction

Over 50 years since Huggins and Hodges first recognized the hormonal dependence of prostatic cancer [1], hormonal therapy is still central to the management of advanced disease [2]. The response to treatment is temporary, with relapse occurring usually within 2 years in patients with metastases; relapse after hormone therapy is usually fatal within a matter of months [3]. Since its introduction, there has been a debate about the optimal timing of hormonal therapy [4]. Advanced prostatic cancer is treated at diagnosis in the hope of delaying the onset of symptoms and it may well prolong survival, although this has been questioned [5].

Alternatively, the patient may be treated when symptoms occur and if he responds a further asymptomatic period will follow, with survival possibly similar to that occurring with immediate treatment [6]. An elderly man may die from an unrelated cause before he develops symptoms requiring treatment. Thus, unless early treatment can be shown to have advantages, deferment until a definite indication arises might be preferable [7]. The Veterans Administration Cooperative Research Group (VACURG) studies included randomized control groups treated initially with a placebo but in whom active treatment was allowed on progression. Reviewing these studies, Byar [6] stated 'These data support the concept that treatment can be delayed ....'.

In 1985, the MRC commenced a trial to compare immediate and deferred hormone treatment in patients with locally advanced or asymptomatic metastatic prostate cancer. Recruitment into this study was closed at the end of 1993 and this paper reports its first results.

Patients and methods

The study was designed to assess the impact of hormonal treatment commenced at the time of diagnosis on the

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*See Appendix 1

course of the disease, compared with delay in treatment until clinical progression occurred. Participants otherwise managed their patients according to their clinical practice. In the hope that a substantial number of busy working urologists could be recruited, entry and follow-up were simplified as much as possible, and only data considered relevant to the main issue were collected. Patients were registered and randomized by a single telephone call to the trial office. Annual follow-up information was collected using simple forms sent from the trial office to the participating clinician at the appropriate time.

Eligibility of patients

Histological evidence of adenocarcinoma of the prostate was essential; some participating urologists were accustomed to making therapeutic decisions on the basis of reliable fine-needle aspiration cytology. If such a participant wished to randomize a patient before TURP, so that if immediate treatment was drawn an orchidectomy could be performed at the same time, provisional entry and randomization was accepted, provided that this was followed by later histological confirmation. Patients could undergo a therapeutic or diagnostic TURP and were still eligible if they received radiotherapy to the prostate, but were not included in the numbers for local progression. The patient had to have either local disease considered too advanced for curative treatment (i.e. T2–T4) or metastatic disease not causing symptoms. Patients had a ECOG performance status of 0–2 and no other immediately life-threatening disease, with an expected survival $\geqslant 12$ months. Patients were ineligible if they had received previous hormonal treatment. Eligibility was otherwise governed by the 'uncertainty principle' — if both the clinician and patient were substantially uncertain whether immediate hormonal treatment was appropriate, then the patient was eligible for entry.

Randomization

During the registration/randomization telephone call, essential baseline details were recorded on computer and a 'minimization' algorithm [8] used to limit chance differences between groups in age, T category and metastatic status. Those randomized to immediate treatment were required to commence hormone therapy within 6 weeks of entry. Patients allocated to deferred treatment were followed up according to the practice of the participant until an indication to commence hormone treatment occurred. Indications for treatment in deferred patients were at the discretion of the participant.

Treatment

The original protocol specified orchidectomy (total or subcapsular) as the method of androgen deprivation. When the trial began, LHRH analogue drugs were not available for routine prescription but once they were licensed and shown to be therapeutically equivalent to orchidectomy [9], it was considered unreasonable to deprive patients eligible for the study of this alternative. The protocol was modified to allow either orchidectomy or an LHRH analogue, according to the physician's and patient's choice. If an LHRH analogue was chosen, tumour-flare protection with an anti-androgen was recommended. If for any reason either of these options became inappropriate, an alternative form of effective hormone therapy was allowed.

Follow-up

Patients were followed according to the participant's usual practice. Each year, shortly after the anniversary of entry, a simple one-page enquiry form was sent from the trial office, requesting information confirming treatment had taken place in immediate patients, the date and reason for treatment in deferred patients and information about the progression of the patient's disease, with specific questions concerning the need for TURP for local progression, development of metastases in M0 patients and complications such as spinal cord compression, pathological fractures, ureteric obstruction and development of extra-skeletal metastases. Information on dates and causes of death was also obtained from National Health Service records.

Metastatic disease

As an aid to recruitment, it was intended to simplify registration and to allow investigators to adopt as much of their routine practice as possible. It transpired that many British urologists did not have ready access to bone-scan facilities. Thus, the simple stratification into M0 and M1 disease envisaged in the protocol had to be modified. An additional category, Mx, was introduced and the categories defined as: M0, patients with no evidence of metastatic disease, confirmed by a negative bone scan; Mx, patients with no evidence of metastatic disease, but with no confirmation by a bone scan; M1, patients with definite scintigraphic, radiological or other evidence of metastatic disease.

Statistical methods

Patients remained in their originally allocated treatment group, regardless of whether the allocated treatment was

adhered to. Thus, the trial did not compare two treatments (all immediate against all deferred) but compares two treatment policies, sometimes called an 'intention to treat' analysis [10]. Although it has the disadvantage that if a few patients do not comply with their allocated treatment any real differences in outcome will be diluted, it has the advantage of avoiding bias, so if any definite differences in outcome are found, they must be real. Events such as the development of complications from local progression and from metastatic disease are analysed by a simple comparison of the total numbers affected; standard Kaplan-Meier survival curves and log-rank methods [11] were used to analyse times to treatment, times to progression and times to death. Two-sided P values ($2P$) are cited throughout, with $2P > 0.05$ taken to indicate no significance. Where survival data are discussed in the text, the quoted P values are those of the survival curves, not the crude proportions dead.

The protocol envisaged a target of 2000 patients; during recruitment, the interim results were reviewed regularly but were not made available to the participants. No clear differences emerged from the interim results to suggest ending the study, but because recruitment declined gradually, it was decided to close entry on 31 December 1993 and this report is based on follow-up data available at 1 August 1996. The protocol was approved by the participant's local ethical committee, with whom the information and consent form was agreed. Patients undergoing orchidectomy, in addition to consent to trial entry, signed an operation consent form.

Results

A total of 938 patients were recruited (Table 1) and results reported for the 934 patients (469 treated immediately and 465 deferred) on whom follow-up data were available.

Fifty-one patients randomized to deferred treatment were recorded as dying from causes other than prostate cancer before an indication for treatment arose (Table 2); 29 had confirmed M0 disease, 16 were Mx and only six were M1 at randomization. Of the 131 deferred patients aged <70 years at randomization, only five (3.8%) died from other causes before needing treatment, compared with 20% of men aged $\geqslant 80$ years. Twenty-nine deferred patients died from prostate cancer (and two from unknown causes) having received no form of hormonal treatment.

Table 1 Patients with follow-up information available (total numbers recruited are shown in brackets)

	Immediate	*Deferred*
M0	256 (256)	244 (247)
Mx	83 (83)	90 (91)
M1	130 (130)	131 (131)
Total	469 (469)	465 (469)

Table 2 Death from other causes before treatment in deferred patients

Age at randomization (years)	*No. randomized*	*No. of deaths*
<60	10	1
60–64	41	0
65–69	80	4
70–74	116	10
75–79	136	20
80+	82	16

Treatment

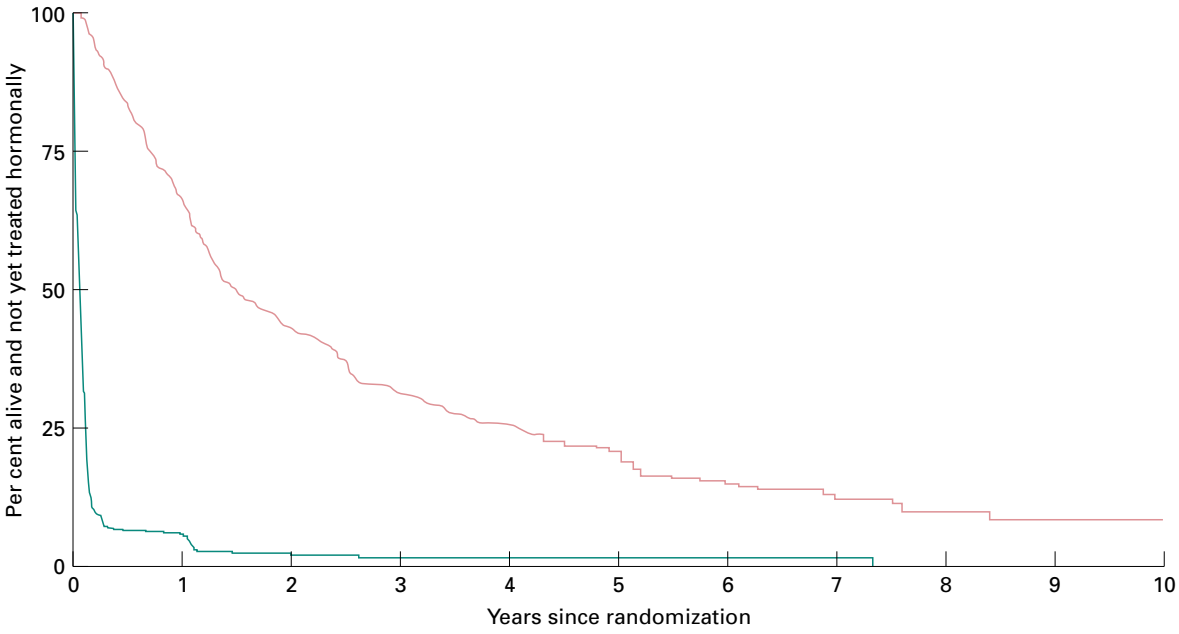
Of 469 patients randomized to immediate treatment, 460 received hormonal treatment, generally within the 6-week period laid down in the protocol. Of 465 patients receiving deferred treatment, 347 have now undergone treatment (Fig. 1). Of 131 deferred patients with confirmed metastases (M1), 119 underwent treatment, 50% within 9 months of randomization. In deferred patients with confirmed non-metastatic disease (M0), 169 of 244 patients were treated, 50% within 27 months (Fig. 2); Table 3 lists the treatments used. Overall, 98% of patients treated received one of the options specified in the protocol, although this fell to 95% in those receiving deferred treatment.

Deferred treatment was started almost as commonly for problems related to local progression as it was for metastatic disease (Table 4). Increasing levels of tumour markers were a more recent indication, presumably due to the introduction of PSA measurements into clinical practice during the course of the study.

Progression

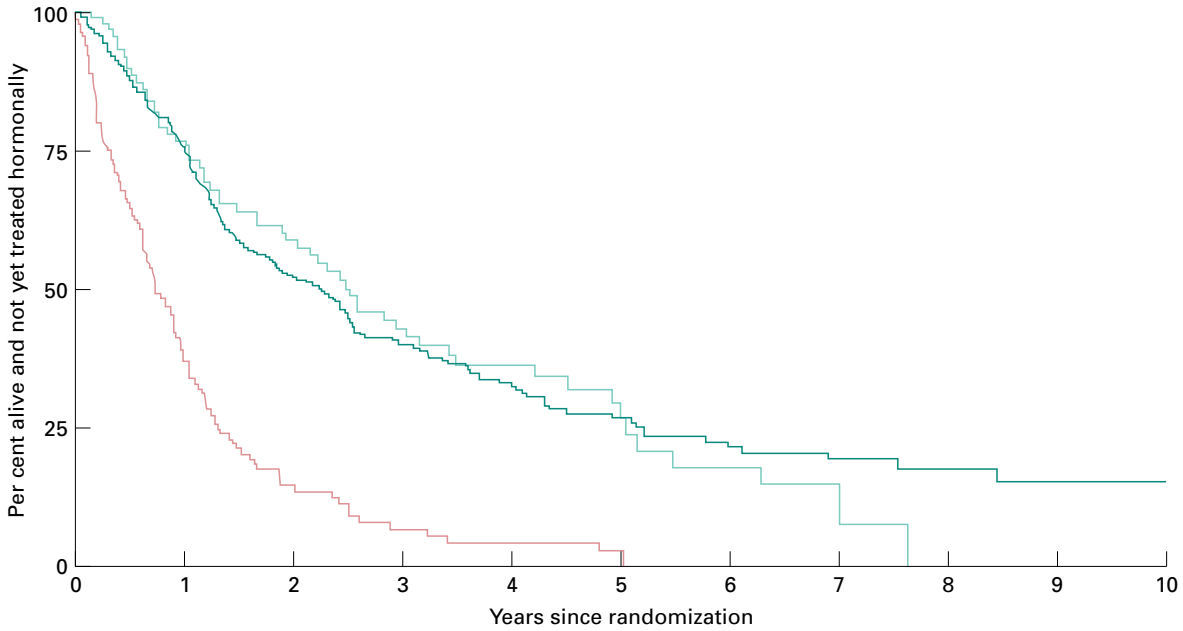
For distant progression, of those allocated immediate treatment, 96 patients with M0 disease developed metastatic disease or died from prostate cancer, compared with 144 when treatment was deferred (Fig. 3, $2P < 0.001$). Overall, 121 patients treated immediately (37 with M0 disease) developed pain from metastatic disease, compared with 211 (84 with M0) in the deferred arm (26% and 45%, respectively, $2P < 0.001$).

For local progression, 65 patients in the immediate arm underwent a TURP during follow-up, compared with 141 in the deferred group ($2P < 0.001$). The proportions were similar whether or not the patient had



At risk:											
Immediate	469	24	7	5	2	1	1	1	0	0	0
Deferred	465	288	169	110	78	47	28	16	8	6	2

Fig. 1. Time to commencing hormonal treatment (orchidectomy or LHRH analogue) for all patients, by randomization group. Green, immediate. Red, deferred.



At risk:											
M0	244	177	111	78	56	34	22	14	8	6	2
MX	90	64	44	29	19	11	6	2	0	0	0
M1	131	47	14	5	3	2	0	0	0	0	0

Fig. 2. Time to commencing hormone treatment; deferred patients, by metastatic status on entry. Dark green, MO. Light green, MX. Light red, M1.

Table 3 Type of hormone treatment given

	Immediate	*Deferred*
Orchidectomy	411	248
LHRH analogue	47	82
Cyproterone acetate	1	12
Oestrogens	1	4
Flutamide		1

Table 4 Indications for treatment in patients randomized to deferred treatment (more than one indication was recorded for some patients)

Pain from or complications of bone metastases	181
Local progression	159
Increasing tumour marker level	24
General systemic effects	25
Patient preference	5
Not known	4

undergone a TURP before entry. Thirty-three patients in the immediate arm and 55 in the deferred arm developed ureteric obstruction (Table 5).

Complications

Spinal cord compression, pathological fractures and extra-skeletal metastases occurred more commonly in deferred patients (Table 5), the overall incidence of serious complications being about twice as high in patients in whom treatment was deferred. The higher incidence of complications in deferred patients was more apparent in those presenting with metastatic disease.

Mortality

Overall, 67% of deaths during the study were ascribed to prostate cancer (Table 6); 328 patients died in the immediate and 361 in the deferred group (Fig. 4, $2P = 0.02$), with 203 deaths in the former and 257 deaths in the latter from prostate cancer (Fig. 5, $2P = 0.001$). Differences in mortality were not statistically significant in patients with M1 or Mx disease. For patients with confirmed M0 disease, survival curves are shown for overall survival (Fig. 6, $2P = 0.02$) and for deaths from prostate cancer (Fig. 7, $2P < 0.001$). Where the cause of death was unknown, the patients were included in the deaths from prostate cancer. For M0 patients, there were five deaths from unknown causes in the immediate

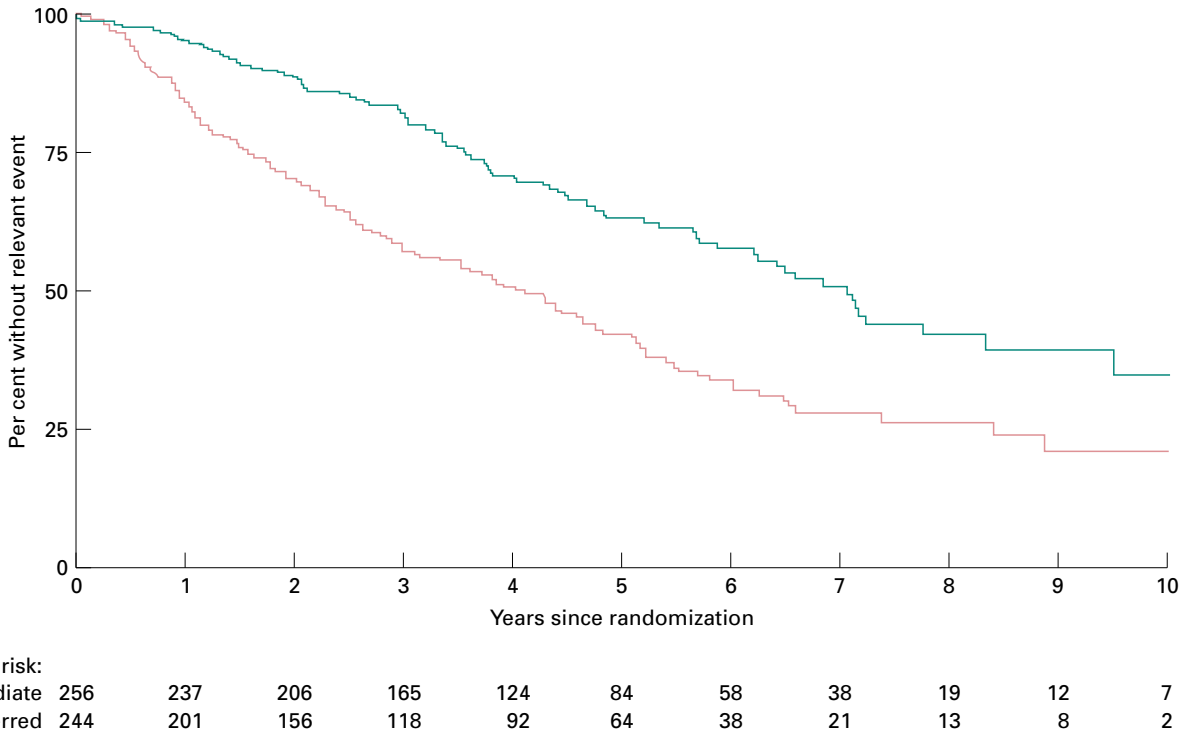


Fig. 3. Time to distant disease progression, or death from prostate cancer: patients entered as non-metastatic (M0), by randomization group (96 of 256 immediate and 144 of 244 deferred treatment; log-rank [O–E] = 40.3 with variance 58.5; $2P < 0.001$). Green, immediate. Red, deferred.

Table 5 Major complications

	Immediate (n = *469*)	*Deferred* (n = *465*)
Pathological fracture		
M0	3	6
Mx	1	4
M1	7	11
Total	11	21
Cord compression		
M0	3	3
Mx	1	6
M1*	5	14
Total†	9	23
Ureteric obstruction§		
M0	22	28
Mx‡	1	12
M1	10	15
Total†	33	55
Extra skeletal metastases		
M0	17	26
Mx	7	9
M1	13	20
Total*	37	55

*$2P < 0.05$; †$2P < 0.025$; ‡$2P < 0.005$; otherwise statistically not significant. §Excludes seven patients receiving local radiotherapy to the prostate.

Table 6 Causes of death

	Overall (n = *934*)	*Immediate* (n = *469*)	*Deferred* (n = *465*)
All deaths			
M0*	321	150	171
Mx	144	67	77
M1	224	111	113
Total*	689	328	361
Deaths from prostate cancer‡ (% of all deaths)			
M0†	200 (62)	81 (54)	119 (70)
Mx	86 (60)	38 (57)	48 (62)
M1	174 (78)	84 (76)	90 (80)
Total†	460 (67)	203 (62)	257 (71)

*$2P < 0.01$; †$2P < 0.001$ for immediate versus deferred treatment; otherwise statistically not significant. ‡Includes 17 deaths from unknown causes (see text).

group and three in the deferred group. If the latter three had died from other causes (the most extreme possibility) this would not materially effect the significance level of the prostate cancer deaths. Figure 8 shows deaths from causes other than prostate cancer ($2P = 0.05$)

Discussion

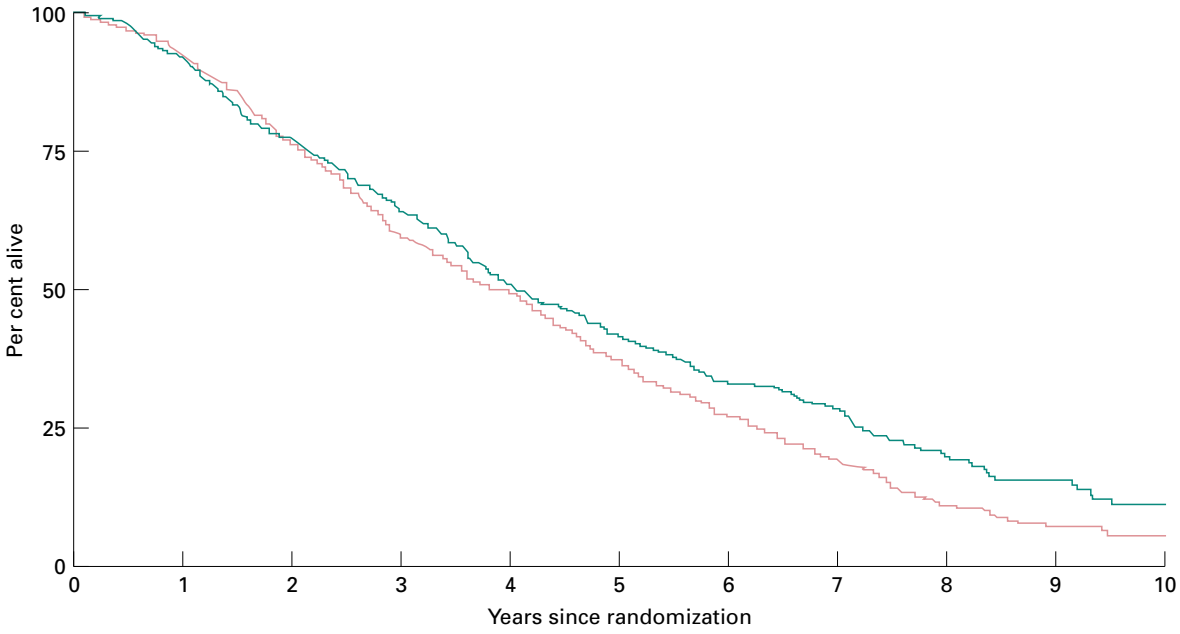
The concept of deferring treatment in patients with asymptomatic advanced prostate cancer was encouraged by the VACURG studies [6]. Not only did these show no clear disadvantage in terms of survival from delaying treatment, but also suggested that many patients with advanced prostate cancer died from other causes; indeed overall, of those dying during the VACURG studies, only 41% died from prostate cancer. Ever since hormonal treatment was introduced, it has been questioned whether treatment started when the disease is diagnosed prolongs life compared with treatment deferred until progression occurs [2,12]. Recently, there has been more doubt about the justification for deferring hormonal therapy [13] and it has been argued for almost half a century that to defer treatment risks the loss of hormone sensitivity in the tumour [2,14].

Even if deferring treatment has no effect on survival, concern has been expressed that delaying treatment will cause other problems. Clinical impression suggests that many untreated men will develop recurrent bladder outflow obstruction or worse, obstructive uraemia, although local progression can probably be controlled as well by radiotherapy as by systemic hormone treatment [15]. There is also concern that serious complications such as spinal cord compression might occur unheralded by other symptoms in untreated patients. The trial protocol addressed these issues as well as the simple question of survival.

The design of this study is unusual in its attempts to simplify trial participation and allow the management of patients to follow the normal practice of the participant, except for those issues essential to the question being investigated. This gives a loose structure compared with more conventional studies but was considered essential if the trial was to be supported by the urologists in district general hospitals who manage most men with prostate cancer in the UK. Also, this type of design gives results that are more applicable to routine practice when compared with a rigid protocol which may only attract a selected group of patients managed under unusual circumstances.

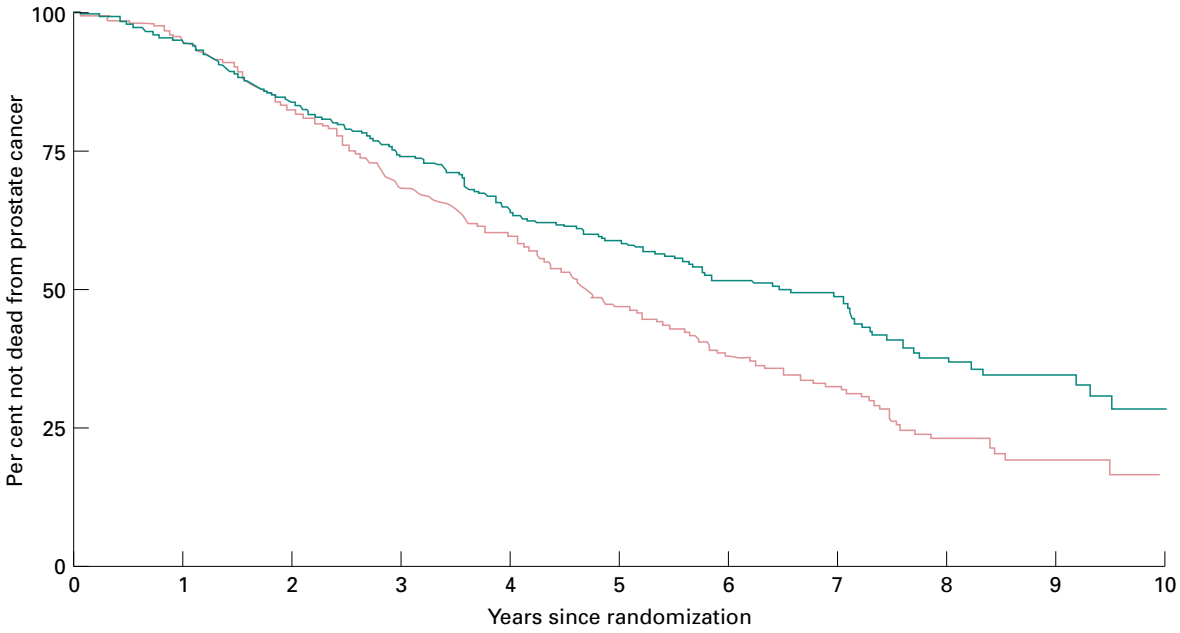
Staging classification

The protocol did not specify a bone scan in all patients, as this information would not be necessary to define M1 disease in a patient who had clear *radiological* evidence of metastases. It was not appreciated until the trial was underway that at that time many British urologists had no easy access to nuclear medicine facilities. Thus, patients were being classified as 'M0' without having had a bone scan. As some of those participants



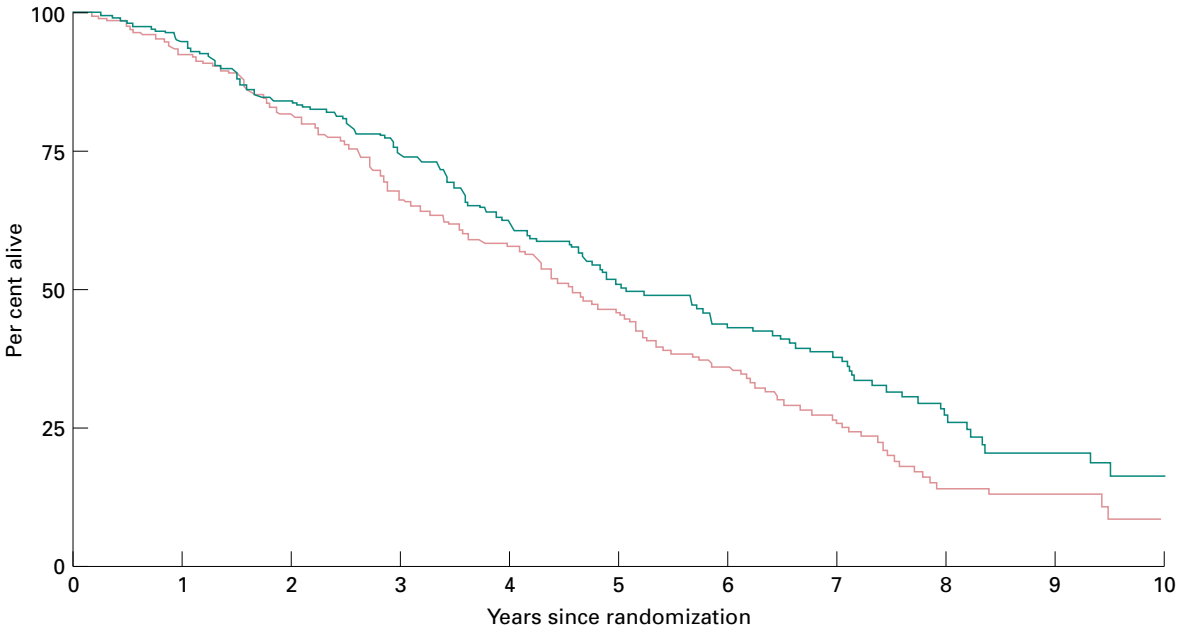
At risk:											
Immediate	469	430	358	280	205	150	102	73	39	23	11
Deferred	465	430	349	260	207	136	85	51	27	14	5

Fig. 4. Time to death from any cause: all patients, by randomization group (328 of 469 immediate and 361 of 465 deferred treatment; log-rank [O–E] = 30.1 with variance 171.2; $2P = 0.02$). Green, immediate. Red, deferred.



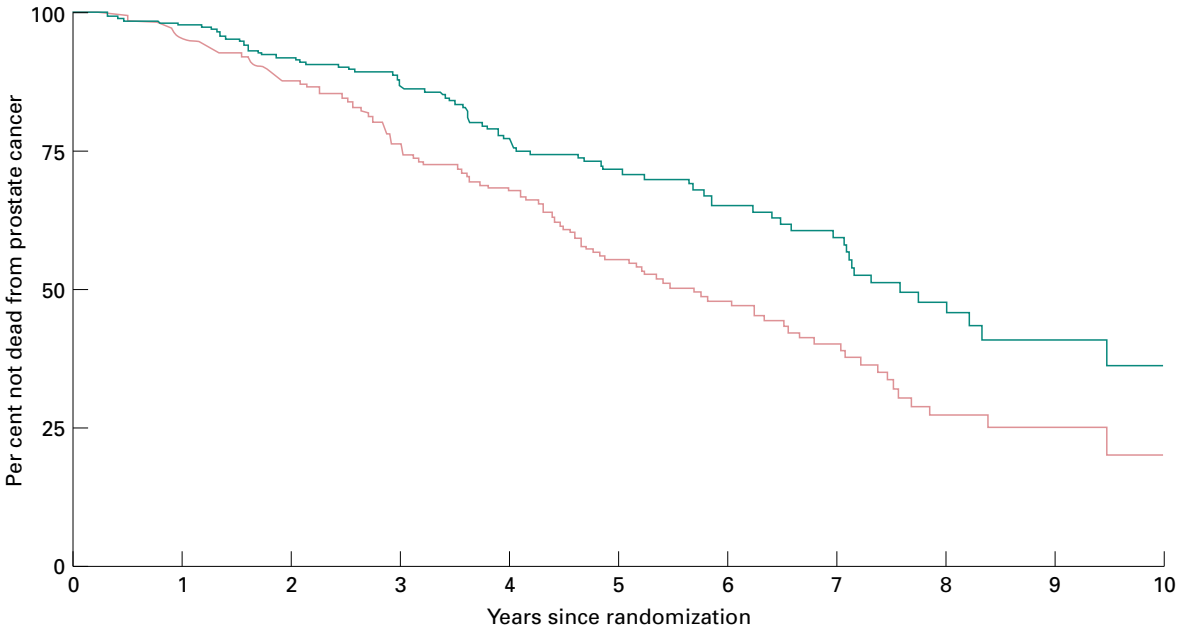
At risk:											
Immediate	469	430	358	280	205	150	102	73	39	23	11
Deferred	465	430	349	260	207	136	85	51	27	14	5

Fig. 5. Time to death from prostate cancer: all patients, by randomization group (203 of 469 immediate and 257 of 465 deferred treatment; log-rank [O–E] = 35.2 with variance 114.4; $2P = 0.001$). Green, immediate. Red. deferred.



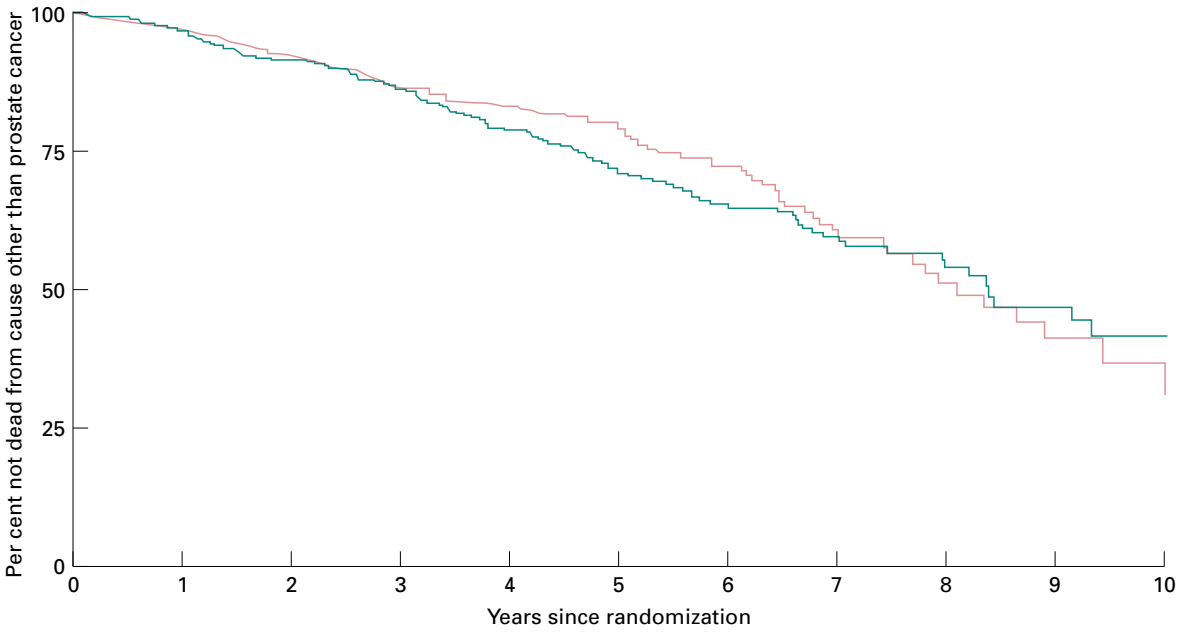
At risk:											
Immediate	256	243	212	172	133	93	65	45	23	13	7
Deferred	244	227	197	153	124	86	57	34	15	11	4

Fig. 6. Time to death from any cause: patients entered as non-metastatic (M0), by randomization group (150 of 256 immediate and 171 of 244 deferred treatment; log-rank [O–E] = 20.6 with variance 79.7; $2P = 0.02$). Green, immediate. Red, deferred.



At risk:											
Immediate	256	243	212	172	133	93	65	45	23	13	7
Deferred	244	227	197	153	124	86	57	34	15	11	4

Fig. 7. Time to death from prostate cancer: patients entered as non-metastatic (M0), by randomization group (81 of 256 immediate and 119 of 244 deferred treatment; log-rank [O–E] = 25.4 with variance 49.6; $2P = 0.0003$). Green, immediate. Red, deferred.



At risk:											
Immediate	469	430	358	280	205	150	102	73	39	23	11
Deferred	465	430	349	260	207	136	85	51	27	14	5

Fig. 8. Time to death from causes other than prostate cancer: all patients, by randomization group (125 of 469 immediate and 104 of 465 deferred treatment; log-rank [O–E] = −5.1 with variance 56.8; $2P = 0.5$). Green, immediate. Red, deferred.

contributing many patients to the trial were in this position, and this reflected current British practice, whether desirable or not, the trial organizers felt that the situation should be accepted. Thus, an Mx category was included, whose overall progress still could be compared except for those aspects where absolute recognition of the metastatic status was essential.

Study treatment

The study concerned the timing of hormonal therapy and was not specifically concerned with one treatment modality. The simplest design would have been to allow the participant (and the patient) a totally free choice of hormonal treatment, but this might have led to instances of suboptimal treatment or to possible confusion if some patients received maximal androgen blockade. The study started before any LHRH analogues had received licences, when orchidectomy was favoured by most British urologists and was chosen as the preferred method of treatment. When LHRH analogues were licensed and shown to be therapeutically equivalent, the option of either treatment was introduced into a revised protocol. Despite this, orchidectomy remained the predominant choice (Table 3). The lower proportion of patients undergoing orchidectomy in the deferred group partly reflects the fact that more of them were starting treatment after the protocol was amended. Also, deferred treatment for a symptomatic indication often needs to be commenced promptly, when immediately available medical treatment may have an advantage over a surgical procedure requiring hospital admission. The possibility that someone other than the original trial participant might be caring for the patient when the indication for deferred treatment occurred may account for the larger number of deferred patients receiving non-standard treatment. Clearly, all treated patients have received effective hormonal therapy and the comparability of different methods of androgen deprivation make it unlikely that any difference in outcome will have resulted from the asymmetry in methods of treatment.

Outcome

Overall, 11% of deferred patients died from unrelated causes before an indication for treatment arose. This could be considered the main success of a policy of deferred treatment; those most likely to benefit in this way from deferred treatment are elderly men with non-metastatic disease. Most men aged <70 years developed an indication for treatment during their lifetime. However, a further 5% died from prostate cancer before treatment was started, a risk of deferred treatment highlighted by previous authors [16]. Of all those dying,

67% did so from prostate cancer; this compares with 41% in the VACURG studies [6] and reflects, in part, the improving life expectation of elderly men.

As expected, and as reported in previous studies, progression of disease will be arrested or slowed in patients treated immediately. This was manifested by a more rapid development of metastatic disease in patients with M0 disease at presentation (Fig. 3) and earlier onset of bone pain in those for whom treatment was deferred; in addition, local progression was more rapid. The clinical impression that more TURPs are needed in men for whom treatment is deferred has been confirmed, with 141 deferred patients requiring TURP compared with 65 of those treated immediately. Local progression was almost as common an indication as metastatic disease for starting treatment (Table 4). More seriously, ureteric obstruction was more likely to occur in deferred patients (Table 5).

The most serious, potentially catastrophic, complications of metastatic carcinoma of the prostate are spinal cord compression and pathological fractures. These occurred in 44 of 465 patients in whom treatment was deferred, compared with 20 of 469 who were treated immediately. Spinal cord compression often occurred *after* treatment had already been started for another indication and may be due to an increased burden of metastatic disease developing during the period without treatment, rather than occurring unheralded with no previous warning symptoms. At present, the increased risk of these complications is most marked in patients with metastases at presentation. This may partly reflect the immaturity of the data for M0 patients. However, the need for treatment arose after a median of 9 months in men presenting with metastatic disease, and few escape treatment before they die. Thus, the avoidance of side-effects of hormonal treatment for a mean of 9 months has to be balanced against the risk of important complications.

Survival

Although overall survival was significantly longer in patients treated immediately (Fig. 4), the difference was more marked for deaths from prostate cancer (Fig. 5). This difference is largely due to patients with M0 disease (Figs 6 and 7), although the data for this group are still comparatively immature, as to date only 64% of patients have died. The relatively few patients with metastatic disease at presentation, their more rapid death rate and the short median interval to treatment in deferred patients may explain why it is difficult to identify a difference in their survival.

Although these data show a relatively large difference in deaths from prostate cancer (Fig. 5) because the patients were elderly, half the patients would, if they had not developed prostate cancer, still have died from other causes during this period (Fig. 8). Hence, the highly significant difference in prostate cancer survival is about twice as great as the difference in overall survival (Fig. 4). There is no evidence to suppose that orchidectomy or LHRH analogues will increase other causes of death, as happened with oestrogens in the VACURG studies [6]. As the study was not blind, a bias could occur in ascribing death to prostate cancer more often in deferred patients, but there is no significant evidence of this (Fig. 8) and there is in any case a significant difference in overall survival. Thus, immediate treatment significantly delayed deaths from prostate cancer and this appears to have about as great an effect on overall survival as should be expected in this age group. Although this improvement in survival is not large, it still represents an important benefit from immediate treatment, particularly for patients without metastases at the time of diagnosis.

In conclusion, it may still not be possible to make an absolute recommendation applicable to all men with prostate cancer, but the data presented in this paper provide consistent support for the benefits of immediate treatment. The more rapid local and distant progression occurring when treatment was deferred had significant clinical effects in terms of an increased need for TURP, earlier onset of symptoms, and most importantly, a greater risk of important complications such as spinal cord compression. The survival data are perhaps the first clear evidence from a comparative study that early hormone treatment has an effect on mortality. However, for about 10% of patients, treatment does not become necessary during their lifetime. This benefit is unlikely in a younger patient, but for an elderly man with non-metastatic disease, deferred treatment probably remains an option. Certainly, the data presented in this paper can be usefully presented to asymptomatic patients with advanced prostate cancer during discussions with them about their treatment.

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See Appendix 1.
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Appendix 1

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